SCIENTIFIC LETTER

Myocardial late gadolinium enhancement is associated with raised serum amino-terminal propeptide of type III collagen concentrations in patients with hypertrophic cardiomyopathy attributable to the Asp175Asn mutation in the α tropomyosin gene: magnetic resonance imaging study

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Myocardial late gadolinium enhancement in magnetic resonance imaging (MRI) has been proposed to detect myocardial fibrosis in patients with cardiomyopathies, including hypertrophic cardiomyopathy (HCM).[1 2] The amino-terminal propeptide of type III collagen (PIIINP) reflects synthesis or turnover of soft-tissue collagen and is a marker of collagen scar formation after acute myocardial infarction.[3] No studies have investigated the association of myocardial late gadolinium enhancement with PIIINP concentration in patients with HCM. We therefore investigated the relationship of myocardial late gadolinium enhancement by MRI with serum concentration of PIIINP and other markers of collagen metabolism in patients with HCM attributable to an identical HCM-causing mutation, Asp175Asn in the α tropomyosin gene (TPM1).[4]

PATIENTS AND METHODS

The present study enrolled 21 adult patients (9 men, 12 women, mean age 37 years) with the Asp175Asn mutation of TPM1.[4] Seventeen healthy control participants matched for age and sex were also enrolled.

MRIs were acquired with a 1.5 T clinical scanner (Magnetom Vision; Siemens Medical Systems, Erlangen, Germany) in the left ventricular (LV) short-axis orientation. Late-enhancement images were acquired at the level of the tips of the mitral valve leaflets and at the level of the papillary muscles with a T1-weighted single-shot inversion-recovery fast low angle shot sequence 10–15 min after gadopentetate dimeglumine (Magnevist; Schering AG, Berlin, Germany) injection into the antecubital vein (0.05 mmol/kg body weight).

LV short-axis images at the levels of the tips of the mitral valve leaflets and papillary muscles were divided into the anterior and posterior septum and LV free wall. In each segment, the visually brightest and darkest regions of myocardium were selected and manually outlined. Signal intensity (SI) (arbitrary units) in these two regions and epicardial fat were measured with Cheshire V.1.18 software (Hayden Image Processing Group, Boston, Massachusetts, USA). Segmental late-enhancement heterogeneity was determined by subtracting the lowest SI value from the highest SI value in each segment and normalising the difference to epicardial fat by the equation $((SI_{highest} - SI_{lowest})/SI_{epicardial\ fat}) \times 100$.

Venous blood samples were obtained after a 12 h fast. Markers of collage metabolism (PIIINP, carboxy-terminal propeptide of type I collagen (PICP), amino-terminal propeptide of type I collagen (PINP) and carboxy-terminal telopeptide of type I collagen (ICTP)) were analysed with commercially available radioimmunoassays (Orion Diagnostica, Espoo, Finland).

Variables with skewed distribution were analysed after logarithmic transformation in the t test and linear regression. Unpaired t test, Spearman's correlation coefficient, test for linear association, one-way analysis of variance followed by the Scheffé test, and univariate and multivariate linear regression analyses were used when appropriate.

RESULTS

None of the patients with HCM had a history of heart failure. About one third of the patients were taking cardiac drugs. None of the patients with HCM had a significant LV outflow tract obstruction (> 30 mm Hg) on echocardiography. None of the 18 patients with HCM who underwent coronary angiography had a significant coronary stenosis.

On MRI, LV maximum wall thickness was increased in patients with HCM compared with controls (19.4 (SD 5.1) *v* 9.7 (1.7) mm, $p < 0.001$). LV mass index or global ejection fraction did not differ between the study groups (data not shown). Patients with HCM had smaller LV end diastolic and end systolic volume indices than did the control participants (data not shown).

Patients with HCM had higher late-enhancement heterogeneity than the control participants at the papillary muscle level (12 (7)% *v* 7 (3)%, $p < 0.01$), but not at the level of the mitral valve leaflets (data not shown). Of 21 patients with HCM, only five had late-enhancement heterogeneity values exceeding the mean late-enhancement heterogeneity of the control group by two standard deviations or more.

PIIINP concentration was higher in patients with HCM than in control participants (3.60 (1.35) μg/l *v* 2.78 (0.85) μg/l, $p < 0.05$), whereas PINP, PICP and ICTP concentrations did not differ (data not shown). In patients with HCM, PIIINP concentration significantly correlated with late-enhancement heterogeneity ($r = 0.656$, $p < 0.01$). In patients with HCM from the lowest to the highest tertile of late-enhancement heterogeneity, PIIINP was 2.84 (0.94), 3.54 (0.72) and 4.46 (1.93) μg/l ($p < 0.01$) (fig 1). Compared with controls, only patients with HCM in the highest tertile of

Abbreviations: HCM, hypertrophic cardiomyopathy; ICTP, carboxy-terminal telopeptide of type I collagen; LV, left ventricular; MRI, magnetic resonance imaging; PICP, carboxy-terminal propeptide of type I collagen; PIIINP, amino-terminal propeptide of type III collagen; PINP, amino-terminal propeptide of type I collagen; SI, signal intensity

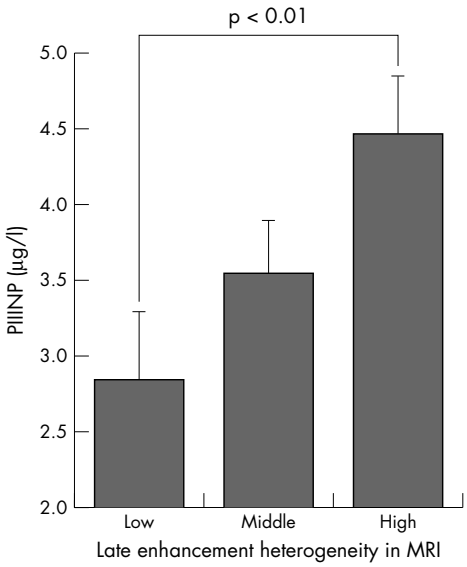

Figure 1 Serum amino-terminal propeptide of type III collagen (PIIINP) concentrations among patients with hypertrophic cardiomyopathy according to tertiles of late-enhancement heterogeneity in magnetic resonance imaging (MRI).

late-enhancement heterogeneity had a significantly different PIIINP concentration ($p < 0.05$).

In univariate linear regression analyses, late-enhancement heterogeneity on MRI ($r = 0.485$, $p < 0.05$), age ($r = -0.565$, $p < 0.01$), diastolic blood pressure ($r = -0.443$, $p < 0.05$) and LV mass index ($r = 0.439$, $p < 0.05$) were significantly associated with PIIINP concentration in patients with HCM. In multivariate regression analysis, only age ($\beta = -0.487$, $p < 0.05$) and late-enhancement heterogeneity on MRI ($\beta = 0.381$, $p < 0.05$) contributed independently to PIIINP variability in patients with HCM. The model explained 46% of PIIINP variability, with age contributing 32% and late-enhancement heterogeneity on MRI 14% to the total variability.

DISCUSSION

We found that patients with HCM attributable to the Asp175Asn mutation in the TPM1 gene had increased late-enhancement heterogeneity on MRI at the level of the papillary muscles. Myocardial late-enhancement heterogeneity was highly variable, in agreement with the findings of Moon *et al*.[2]

In the present study, PIIINP but not ICTP, PINP, or PICP concentration was raised in patients with HCM. In a previous study patients with HCM had increased concentrations of PIIINP and ICTP.[5] Furthermore, we found that concentrations of PIIINP and myocardial late-enhancement heterogeneity were significantly associated.

A limitation of our study is that the number of patients with HCM was relatively small, so that the results of the present study may not be applicable to all patients with HCM. However, both myocardial late enhancement and raised PIIINP concentrations have been found in non-genotyped patients with HCM.[1 5] Raised PIIINP concentrations therefore probably reflect myocardial fibrosis in HCM caused by different sarcomeric genes.

We conclude that in patients with HCM attributable to an identical HCM-causing mutation in the α tropomyosin gene, myocardial late gadolinium enhancement on MRI is associated with PIIINP concentrations.

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The study protocol was approved by the ethics committee of the University of Kuopio and Kuopio University Hospital. All participants gave written informed consent.

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